REMARKS

The pending claims are 18-23, 25-37.

The rejections extant in the Official Action are responded to as follows.

35 U.S.C. §112, 2nd ¶

Claim 25 is rejected for indefiniteness as over Claim 18, from which it depends.

Applicants have recast Claim 25 as an independent claim, thus freeing it from the restrictions of Claim 18 and obviating any alleged indefiniteness caused by dependency.

Withdrawal of this rejection is requested.

35 U.S.C §103

All pending claims are rejected as obvious.

Two new references are cited: Bakker et al. (*British Journal of Cancer*, 1998, January, *77(1)*, 139-146); and Horiguhi et al. (*Cancer Chemother. Pharmacol.* 1992, *31 (Suppl. I)*, S60-S64). The rejection relies upon their combination along with Kuhl, Gorbunova, and Brem –these last three already of record.

Bakker et al. is employed for its teaching of MMDX. Although the Official Action admits that Bakker et al. does not disclose, among other things, the use of MMDX for treating liver cancer, it nonetheless asserts MMDX to be a "good candidate" for same. We are further told by the Action that dosage levels could be adjusted to obtain reduced hematological effects in keeping with therapeutic levels.

Horiguchi et al. relates to adriamycin with lipidol for hepatocarcinoma. Adriamycin, also known as doxorubicin, is not MMDX. Nonetheless, the Official Action asserts the artisan would use the MMDX of Bakker et al. in lieu of the adriamycin of Horiguchi et al.

Structural relationships between the two compounds are officially propounded as a premise for this exchange.

Kuhl, Gorbunova, and Brem are applied as in prosecution heretofore.

Applicants have carefully dilated upon the official position and submit that one in the art would not interpret the references in the manner proposed, and would not come to the conclusion stated under 35 U.S.C. §103.

Bakker et al.

Despite reliance on Bakker et al. as the primary reference, one in the art would come to a conclusion contrary to that officially proposed. In fact, Applicants submit that the artisan would not deem Bakker et al. particularly relevant to the present invention.

Consider the following:

As the Official Action openly concedes, Bakker et al. does not relate to liver cancer. Nor, consistently, does it relate to intra-hepatic administration. In other words, the primary reference is devoid of features critical to the claims. What, then, does it have to convey to one delving into the problem of concern to the present invention? The Official Action presupposes that Bakker et al. would be of value–and of value as a primary reference at that–merely because it mentions MMDX. But let's look at what Bakker et al. actually describes in this regard.

The patients in Bakker et al. had lung cancer, head and neck cancer, colorectal cancer, cancer of the cervix and adenocarcinoma of unknown provenance. The results reported for MMDX in these instances would not provide the artisan with encouragement of the sort contemplated by the Official Action, let alone guidance under 35 U.S.C. §103. For example, Bakker et al. reports a response rate that was "disappointing low" for MMDX in lung and renal

cancer; indeed, it characterizes the result as "ineffective." For head and neck tumors, cervical cancer, and ACUP, the efficacy of MMDX is reported as "yet unclear" given at least low patient numbers. (See Bakker et al. at DISCUSSION section, page 144, right hand column, 3rd full paragraph starting "In the present study...").

So, rather than viewing MMDX as a compound for which reasonable success would be envisioned for a broad breadth of cancers as the Official Action would have it, Bakker et al. presents decidedly hedged results. Indeed, Applicants submit that the only certainty in Bakker et al. is the uncertainty in the effectiveness of MMDX to different types of cancer. To presume that such occluded teachings would prompt one to use MMDX in liver cancer and expect reasonable success is to engraft what the present inventors have discovered on an otherwise unhelpful reference.

And the new secondary reference to Horiguchi et al. does not cure or ameliorate Bakker et al., but rather perpetuates the operative error aforesaid, i.e. that Bakker et al., despite its own reported ineffectiveness and unclarity, points to reasonable success in applying MMDX to liver cancer and via intrahepatic administration.

Horiguchi et al.:

Horiguchi et al. relates to adriamycin. It in no way mitigates the self-stated uncertainty of Bakker et al. as to the usefulness of MMDX, either against those cancers that Bakker et al. reports problemsome vis-à-vis MMDX, let alone liver cancer to which it is entirely silent.

Indeed, adriamycin is a very different drug than MMDX. Among other critical differences is that of metabolic profile. MMDX is metabolized in the liver to a completely different metabolite using a completely different metabolic pathway than adriamycin. As it

happens, the MMDX metabolite that forms in the liver is more potent than its 'parent' compound and the therapeutic effect is due to this. Adriamycin does not show this pathway and its metabolite(s) is/are not active in this regard. In addition to these differences, adriamycin is a topoisomerase II inhibitor, whereas MMDX is a topoisomerase I inhibitor. Thus the respective biological effects are exerted through very different mechanisms of action.

Indeed, it is believed that the intrahepatic administration, which is claimed, amplifies the potency of the MMDX metabolite, thus advantaging a situation which is otherwise unappreciated by the art cited.

Moreover, Horiguchi et al. teach that adriamycin is administered only in the presence of lipiodol. MMDX on the other hand, as contemplated by the invention, is effective in liver cancer even without its suspension in lipiodol (saline alone being adequate). Its inclusion with lipiodol is merely a separate practice envisioned by the invention.

Combining Bakker et al. with Horiguchi et al. does not lead one to conclude that MMDX, to which Bakker et al. reports disparately mixed results, would show the unexpectedly improved and beneficial outcome provided by the present invention, which utilizes MMDX and intraheptic administration.

Kuhl, Gorbunova, and Brem:

These have been widely discussed and distinguished in previous prosecution, to which reference is made. To summarize those positions for convenience:

Kuhl examines the effect of MMDX on human leukemia and lymphoma cell lines, only. Kuhl, like Bargiotti, does not mention use of MMDX to treat liver cancer. It does not mention selectivity to liver tumors. It does not mention hepatic artery injection. It does not mention dosage levels of MMDX for intrahepatic administration, including the levels now

claimed. It does not implicate the treatment of liver cancer in the context of Bakker et al or otherwise.

Gorbunova teaches adriamycin. To reiterate: adriamycin is not MMDX. Also, Gorbunova effectively teaches away from the benefits associated with the invention. Gobunova reports toxicity for adriamycin up to level of Grade II-IV leucopenia for 50% of patients (3rd page, 4th paragraph "Regarding the toxicity...") which in no way renders obvious the Grade 1 leucopenia resulting with the invention. Additionally, Gorbunova would lead one to employ increased dosages: see "Finding 2." which "suggests the possibility of increasing the total dosage and lengthening the time of intra-arterial infusion." This is in direct contrast to what the present Applicants have discovered and claimed with MMDX, and indeed is diametrically opposed to same.

Moreover, Gorbunova, similar to the ineffectiveness and other deleterious issues reported by Bakker et al. in various instances, clinically reports "no objective responses" in a group of twelve patients with a primary inoperable hepatic carcinoma who received 17 courses of 72-hour adriamycin infusions (2nd page, 4th paragraph from bottom). This is direct contrast to and in now way can be said to presage the present invention, where there is not only a clinical response, but one that response is far superior and unexpected. E.g., two objective tumor responses were observed at 200 mg/m^2 (see page 13, lines 9-10). This translates into a reduction of the initial tumor mass of at least 50%. Indeed, one patient evinced a complete response (Page 13, lines 14-17) from the practice of the invention.

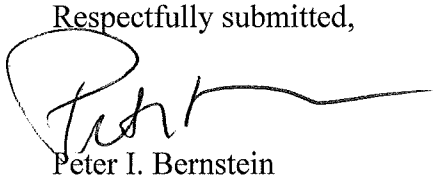
Brem is offered by the Official Action for alleged pulse or short term administrations of chemotherapeutic agents. It thus offers no meaningful input to the above assessment and is discussed *infra*.

The claims are not obvious in view of this art, no matter how that art may be combined. Only Bakker et al. mentions MMDX, but then it only does so in a context that is replete with questions and caveats about its efficacy, and in withal in silence as pertains to human liver cancer. The other references relate to adriamycin. However, this is art-recognized as different from MMDX for reasons *supra*, and even if *pro arguendo* one were to employ MMDX in its stead, as presumably supposed by the Official Action, one would not expect the advantages obtained at the dosage levels claimed. Indeed, in view of Gorbunova, one would reasonable expect either failure ("no objective responses") or significant toxicity (Grade 2-4 leucopenia). These features and attending results of the inventive claims are hallmarks of non-obviousness.

Applicants respectfully request withdrawal of the rejection under 35 USC §103 with passage of the application to allowance.

Applicants encourage an interview on the matter if same would be considered helpful in further elucidating the patentable distinctions. Contact information of Applicants' representative in this regard is provided below.

Respectfully submitted,



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